OFF LABEL AND UNLICENSED DRUG USE IN NEONATAL WARDS (EXCLUDING NEONATAL ICU) AT TYGERBERG CHILDREN'S HOSPITAL (TBH).

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Declaration

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December 2019

Introduction

Off label use of medicines is defined as the use of an authorised medicine for a purpose or in a manner other than that stipulated in the summary of product characteristics (SmPC) (1), or as approved by the medicine control council or authirity of a country (1).The off label use can be for an unapproved indication, for dose, for administering route or, for use in an age group or population not registered during the approval process (2). Unregisterd medicines are medications that have not been approved for medicinal use in a particular country.(1) The majority of medication prescribed to neonates and young infants have not been tested in them and in the European Union 45% to 60% of medicine are given to children off label (3). In the period before 1995 and 2005, only one third of registered medication in Europe were approved for use in children (4), while 54% are approved in the United States of America (4). An Estonian study demonstrated that 80-98% of drugs used in neonates were used off label (5).

The regulation of modern medicine started only after breakthrough progress in the fields of chemistry, physiology and pharmacology (6). This laid a firm basis for medicine testing and research. Certain events such as the diethylene glycol poisoning and thalidomide induced congenital abnormalities in history, also led to establishment of medicine regulatory bodies. In 1937 people in the USA died from diethylene glycol poisoning, which was used as a solvent with no prior safety testing and this led to the establishment of The Federal Food, Drug and Cosmetics act (6). The second important event occurred between 1956 and 1960 and involved the world wide use of Thalidomide (6). Thalidomide was developed in Germany in 1956 and was used as a hypnotic and sedative. Thalidomide's widespread use in more than 46 countries, led to the birth of many babies with phocomelia (6). In 1956, an association was made between Sulfonamide antibiotics use, kernicterus and high rates of mortality in the premature neonate, this was higher than in infants receiving a tetracycline (7). In 1959, a syndrome of sudden cardiovascular collapse was described by Sutherland in three neonates who had received high dose chlorompenicol (8).

Medicine and food regulation bodies were therefore formed worldwide to establish and ensure the safety and efficacy of new medicines, and especially to protect public safety

(6). More recent defining events were the adverse events noted in low birth weight babies who were exposed to parenteral vitamin E (9), a gasping syndrome in those neonates who received excessive doses of benzyl alcohol (10), as well as the roles of maternal retinoic acid and anti-depressants and their link to anomalies in the embryo and fetus. These events affecting the young infant and child, have led to more conservative medicine use and choices by perinatologists, neonatologists and paediatricians (11).

After discovery of a new medicine formulation by a pharmaceutical company, the pharmaceutical company claims temporary legal rights to the formulation (11). Medicine development includes pre-clinical trials, which determine the effects of systemic administration and tolerance, where the chemical formulation is tested on cells and whole tissue prior to testing on animals (12). The medicinal formulation is then taken through further testing phases.

For a medicine to be ideal for children, it needs to be suitable for the age, the physiological condition and body weight of the child being treated (13). Furthermore, the medicine needs to be available in an appropriate form, such as a solid form that can either be taken whole or sprinkled, or a dissolvable form that can be mixed in solution and taken as a liquid mixture or syrup (13).

According to the World health Organisation (WHO), shortage of medicines is a worldwide problem which mostly affects the developing countries (13). There is a worldwide shortage of appropriate medication for children, which unfortunately affects the developing world more profoundly(14). According to The World Health Organisation (WHO), millions of children under five years of age die from diseases that could have been treated had the “ideal medication” been available(14). In December 2007, the World Health Organisation (WHO) launched a campaign called “Make medicines child size” which raised awareness about improving availability of safe, effective and quality medicines for children(14). This initiative was to affect all sectors ranging from government to pharmaceutical companies that are involved in developing and procurement of medicines for children(14). Access to appropriate medicines for children is essential in achieving the World Heath Organisation’s Sustainable development Goals (SDGs), which in 2015 replaced the previous

Millenium Development goals(15,16). MDG 4 and MDG 6 were replaced by SDG 3, where SDG 3.1 aims “By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under 5 mortality to at least as low as 25 per 100 live births” and SDG 3.2 targets that “by 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, waterborne diseases and other communicable diseases” (15,16)

Many medicines in children are used “off label” as there is not enough clinical evidence or trials done on children to support their safety and efficacy therefore, these medicines cannot be registered for paediatric use. The WHO has published guidelines called “Development of paediatric medicines: points to consider in pharmaceutical formulation”. These guidelines seek to provide the ideal children’s medication as stated above, to be suitable for the age, physiological condition and the child’s body size (14). The WHO assistant Director-General for health technology, Dr Howard Zucker said in Geneva in 2007, “We need to learn more about the way children’s bodies react to medicines so we can improve global child health. That’s why it’s extremely important to keep track of potential side effects in child populations. Ultimately, this will save lives and build up a knowledge base for the future” (14)

A wide range of medication prescribed for paediatric patients is done so without any formal study and most are off-label for use in this population (17). Treatment decisions are usually based on the prescriber’s clinical experience, observational studies and at times, extracted from adult data (17, 18). As noted above, this is done because of shortage of clinical evidence. Use of off label or unregistered medication had been linked with paediatric adverse side effects, more than registered medication (17). A study done in Swedish hospitals found that the highest proportion of off-label prescriptions occurred in neonates and infants, 41% of all authorised medicines during the study were given off-label (17). The same study also classified intravenous electrolyte substitutions and carbohydrates as ‘off-label’ as these products were at times used for oral administration though intended for parenteral use(17)

In Europe, the majority of medicines used in paediatrics, have not been studied in this age group and have not been approved by the European Medicines Evaluation

Agency (EMEA) for use in this population (19). Greater caution is needed when prescribing medication for the younger and smaller patient as it may not be appropriate to make decisions based on data gathered from older children and adults (20). Neonates often have different reactions to administered medicines compared to adults, they have unique and rapidly evolving physiological characteristics.(20) Of importance is the understanding of pharmacokinetics, which studies the fate of the medicine as it passes through the living object and Pharmacodynamics which is the link between the dose of the product and its effect on the organism to which it has been administered to (21). A thorough understanding of human developmental biology and an understanding of the dynamic processes of medication absorption, medicine distribution, metabolism and excretion, is the only way that will lead to a more specific approach to neonatal therapeutics.

Children are not small adults but have their own unique physiology, which changes with age groups (22). Neonates and young children have hepatic and renal immaturity which often results in low clearance, inadequate detoxification and the long half-life of particular medicines (20). The various age groups within the peadiatric population itself are not only different in terms of their physical size but, there are also biochemical differences which affect how drugs are metabolized and eliminated via the kidney (22). The pharmacodynamics are marked in the first week of life in a pre-term neonate. The neonate and the young child have higher body water percentage compared to adults, lower proportions of adipose tissue and another difference is that of lower muscle mass (23). An example of the difference in medicine metabolism is that of chloramphenicol in the neonate, this was metioned previously as a cause of high mortality in neonates (22). Studies show increased concentrations of chloramphenicol and its metabolites in the blood of neonates (22). This accumulation is a result of the inadequate process of metabolizing chloramphenicol by glucoronidation, which is age dependent (22). The half life of chloramphenicol varied amoung the age groups, with a half life of twenty six hours in the neonate, ten hours in the infant, and four hours in children (22) Glucuronidation is an important factors in pharmacokinetics (22). The Allometric approach can be used to somewhat predict elimination of medicine but because of lack of accuracy in different age groups, it can not replace clinical pharmacokinetic studies (22). .

The percutaneous barrier is another difference, where the premature neonates has a more thinner percutaneous barrier (stratum corneum) compared to the term neonates (24, 25). Neonates also have increased blood flow to the skin in comparison to adults (24). This affects the amount of medicine absorbed through the skin and the resultant higher systemic availability when compared to the same dose given in adults, where absorption is minimal (26). The pharmacodynamics and kinetics change with maturity, with alteration in protein binding, volume of distribution, renal and hepatic clearance as these systems mature (22). There are also differences between various ages regarding gastric and intestinal emptying time and gastric pH. For absorption to occur, the medication given by extra-vascular route has a number of chemical and physiological steps through which it must go (18). Bio-availability of the substance is affected by changes that occur in the developing gastro- intestinal tract. (18, 20). In a sick individual, physiological changes that occur during illness also affect the absorption of medication.

The oral route is the route of choice whenever appropriate (18). The pH of the stomach contents affects the bio-availability of the medicine (21). The gastric pH changes over time. At birth, it is neutral, decreasing during the first day of life. On the tenth day of life, the pH would have returned to the neutral state (27, 28). In terms of volume of gastric acid secreted, the volume is equal to that of adults by the age of three years (29). By three years of age, the pH is also similar to that of adults (29). These changes therefore render the paediatric patient far different to the adult in that medicines that are affected negatively by gastric pH are absorbed better (29). There is decreased absorption of weak organic acids, some medicines are absorbed more readily and rapidly than in the adult (29). Premature babies differ in that the initial pH changes do not occur in the first fourteen days of life. Gastric emptying in adults occurs in two phase, while in premature infants it occurs in a slower and linear rate. Gastric emptying occurs at the rate of an adult, only by six to eight months of age (21,27, 7). Time taken for intestinal transit, is longer in neonates. This is due to the reduced motility and reduced peristalsis (30). Other differing factors, are immaturity of digestive fluid secretion (21), intestinal mucosa prematurity (28), high intestinal levels of the enzyme beta-glucuronidase activity (28), a reduction in amount of first pass metabolism (21), and variable microbial colonization (21).

A complex amount of developmental processes which are both physiological and biochemical occur during the growth process (31,21). A study done on the effect of phenorbabital in the neonate undergoing thermal therapy also found that the above factors were more important in predicting the clearance of medicines(32). This early period of development entails changes in the volume of distribution, enzymatic activity, elimination pathways, and other variables that change over time (32).

During the first few months of life, there is rapid development in both physiological and biochemical processes, this therefore means that during this time, there is rapid change in medicine pharmacokinetics (31). With these changes it suffices to say that in prolonged therapy in the neonate for example, a neonate being treated for sepsis on day one of life, the pharmacokinetics at the beginning of the treatment, will be very different after two weeks of treatment with the same medicine (31).

There are two phases of medicine metabolism (22). Phase I, is the small structural alterations that occur which aid in the renal excretion by decreasing the lipophylicity of the medicine (22). Phase II “involves the conjugation of a functional group on the molecule with hydrophilic endogenous substrates” Involved in this phase are the processes called acetylation, glucoronidation and sulfation (22). The liver is the most important organ for medicine metabolism, even though so biological transformation occurs in Intestine, skin, kidney and lung (33). Metabolism of some medication, for example, Ibuprofen, requires the Cytochrome P450 complex, components of this system are the CYP2C8 and the CYP2C9 systems, traces of these compounds have been found to be present in the newborn who is younger then one day (34). These amounts increase slowly over the first few weeks of life, to reach half the adult quantity by the time the child is one month of age (34). An example of differing pharmacokinetics is that of isoniazide in the neonate, where neonates were found to have decreased absorption and decreased clearance, this was also noted in the neonate of younger gestational age (35). However, a study of ibuprofen in neonates with a Patent ductus arteriosus had different findings, suggesting that the pharmacokinetics of the ibuprofen were not affected by the gestational age (34)

Generally, most medicines in neonates have a prolonged elimination half-life (35). A

few studies have been conducted to study clearance variability in the neonate (36). One of the studies published in 2005 was based on the clearance of Aminoglycosides, particularly amikacin in neonates. It suggested that the major role players in clearance variability in the extreme premature neonate are the size and post-conceptual age, this therefore raises the need to know target concentrations of amikacin so as to reduce the variability in clearance (36). There is anecdotal suggestion that amikacin is less nephrotoxic in the neonate, as a result of reduced renal uptake capacity (36). The study group hypothesized that the Clearance of medicines and GFR, were also affected by medication given to the mother in the prenatal period, an example of this was the associated rise in GFR at birth in mice that had been given Betamethasone prenatally (36).The clearance of some medication, for example, phenobarbital was found to have a proportional increase with age (32). In the neonate, kidney maturity controls the pharmacokinetics of some medicines such as penicillin, cephalosporins and aminoglycodides (37). In preterm infants, there is reduction in the excretion and clearance when compared to term infants, the clearance of the above medicines is increased with advanced neonatal gestational age and maturation (37). Yet again, isoniazide is an example of differing pharmacokinetics in the smaller and younger patient, where it goes through intensive first pass metabolism (35). Medication elimination rate then, depends on the maturity of the Cytochrome P450 hepatic enzyme system, immaturity of the liver and therefore the liver enzymes will impair the elimination of the medication in the more premature and younger low birth weight infant (35). Another known fact is that of a decreased half-life as the age increases, this supports that there is slower elimination of isoniazide in the young child (35)

Children may have different reactions to medication and the medicine's ingredients when compared to adults (34). Ingredients contained in the medicines given to adults may not necessarily be safe to give to neonates but, medicines that were developed for adults are used in this valnurable age group (34). Attention to the needs of the neonate population, needs to be made a priority in making safe and appropriate medicines (38). There are a number of reasons why conducting clinical trials in children as a whole is difficult (3). Ethical issues arise in choosing the type of randomized control trial to conduct for off label medicines in neonates, these relate to Study design, Subject enrolment, informed consent and data analysis (39). The following is discussion of some of these issues: There are a number of concerns

regarding the present use of off label medicines in neonates without understanding their efficacy and risk, the risks in neonates are higher as this is a critical period of development, associated with fetal programming effect(39). The question therefore, is whether randomized control trials should be done in neonates or whether to continue without being fully aware of safety, pharmacokinetics and efficacy of the medicines we choose.

The Belmont report in 1979 recommended, “Special protection for research involving vulnerable subjects and children”(39). According to the American federal regulations, there are ethical conditions that need to be satisfied before a review board can approve research, the regulations are based on risk, benefit and the likelihood of yielding generalisable knowledge (39). The most important aspect mentioned in the Belmont report, which is important in children is “the benefit issue” the prospect of direct benefit (39). In conducting randomized control trials, the trial needs to be designed in a way that minimizes risks and maximizing benefits (39). There are two types of research designs that are usually used in neonates, active control trials and placebo control trials. Active control trials (ACT), use active controls with equal allocation. Placebo controlled trials (PCT), use placebo with equal allocations (39). Ethics in ACT, involves a comparator rather than placebo. ACTs decrease the risks to the participants and establishes the equivalence or non-inferiority of a new treatment, compared with a tandard treatment (Active control) (39).

PCT, is most commonly used as it determines efficacy and safety. It requires the subject over a shorter period (39). Ethically, a PCT is only justified if no standard treatment exists, if it exists, then the PCT is only justified if no evidence of efficacy or safety has been established; an example of this, was the study of caffeine in neonates (caffeine studies have been published in many countries where Caffeine is not registered, unlike in South Africa). However, PCT in life threatening conditions cannot be justified (39).

Enrolment of subjects poses another ethical issue. Obligation for enrolment consent lies on the treating doctor or the person doing the study. The doctor is obliged to offer the parents an opportunity to enroll the baby in the study. The person doing the study needs to share existing evidence for or against the medicine and compare to other

available treatment (39). Studies done within the first twenty four hours of life need antenatal notification or consent (39).

According to a paper published at George Washington University in 2005, only 2.8% of medicines studied were registered for use in the neonates (11). Between 1995 and 1998, out of the 45 medicines registered by the European Medicine evaluation agency, 29 of these had potential use in the neonate or child, but only 10 of these was actually registered for use. Therefore, 33% of potentially useful medicines were licensed for neonates (11). Between January 1995 and September 2001, 1380 medicines were registered in Europe, 1157 of these had potential use in children and neonates, but only 339 of these were licensed for all children, 257 of them were on-label because of age and weight groups only (11). These show a drop rather than an increase in use of registered medicine, or rather, emphasizes the fact that the amount of studies undertaken for the registering of medicines has decreased (11).

Of interest also are studies that were done to look at the nature of unregistered medicine use and also in which areas of the healthcare system were these medicines being used. A study in the neonatal intensive care units in the United Kingdom showed that within a period of 13 weeks in 1999, 70 patients received medication, of whom 49 were premature and 21 were term neonates (11). In that study, A total of 455 prescriptions were written for the neonates and 45 medicines (10%) of the medicines prescribed were not registered. The unregistered medicines most commonly used in that neonate group was caffeine (11). In the Netherlands, over a 5 week period in 2001, 62% of the prescribed medication was unregistered, with caffeine again being the most frequently used un-registered medication in that study(11).

A study done in Turkish neonatal intensive care units, showed that within a period of 24 hours, of the 1315 prescriptions written up, comprising 93 medicine formulations, 62.3% of the medication given to the neonates were un-registered or off- label (40). A similar study in Germany showed that 61% of all paediatric patients in Germany received at least once in their lives, off label medication. Another study, actually compared use of off label medication between neonates and older children. This study, showed that, off label medication use, was about 80-97% in NICU as opposed to 36-92% in the Paediatric Intensive care unit (40).

The use of unregistered and off label medication in neonates cannot be avoided as it is often necessary to treat medical conditions in neonates. This does not in any way show negligence or poor medical practice as there are often no registered alternative medications that can be used (11). Furthermore, many countries like the United States and Turkey have in their legislation made room for doctors to prescribe, pharmacy to dispense and for nurses to administer un-registered and off label medication when there are no existing alternative options(36,11).

Although there is a lot of concern regarding the use of un-registered and off label use of medicines in neonates, information relating to the extent of this use in South Africa is very limited and for this reason this study was undertaken (41,36).

Aims and objectives

The aim of the study is to determine the off label and unregistered use of medicines in neonates admitted to Tygerberg Hospital..

Primary Objectives

1. To identify the magnitude off-label and unregistered medicines prescribed in the general neonatal wards over a 3-month period.
2. To assess whether these medicines where used off-label for dose, route of administration, indication or frequency.

Methodology

Setting:

Tygerberg Hospital is a tertiary care hospital situation in the Western Cape South Africa. It serves as a referral hospital for approximately half of the Western Cape Province. The Division of Neonataology is situated within the Department of Paediatrics and Child Health and admits approximately 300 neonates to the neonatal intensive care unit and the neonatal wards. This research project was conducted within 3 neonatal wards excluding the neonatal intensive care unit.

Type of study:

This is a prospective descriptive study

Duration of the study:

The study was conducted over a 3 month period (August to November 2013)

Population studied:

Inclusion criteria:

- All neonates (0-28 days old) admitted to the three neonatal wards and who received medicines during the admission.

Exclusion criteria

- Neonates older than 28 days old
- Neonates admitted to the neonatal intensive care unit.
- Neonates who did not receive any medicines during admission.

Data collected and analysis

This was a prospective descriptive survey done over a three months period investigating all medicine scripts of neonates admitted in the study period. Data collected included age, clinical diagnosis, weight on admission and medicines prescribed including dose, formulation, indications and frequency. Excluded from prescription records were Intravenous fluid replacement solutions, mineral supplements, blood products and oxygen therapy. The data (textual and numerical) was captured on a computerised format using a spreadsheet on an IPAD. The data was then be analysed using the medicine package insert pamphlet and the South African Medicines Formulary 2014 and the MIMS (Monthly index of medical specialties) to determine whether they were prescribed appropriately, or off label or unregistered. Registered medication was further subdivided into off label groups, namely, off label for dose, for indication, for frequency, for route of administration, for lack of data or contraindicated in the age group.

A unique study number was assigned to each patient record and this list was kept separate from data capture sheet, where data was collected linked to the unique study number. Data analysis was anonymous using only this unique study number.

Statistical analysis

Descriptive data was analysed reported as means and standard divisions where the data was evenly distributed or otherwise as medians and interquartile ranges. In comparisons between groups Chi square analysis was used.

Ethical considerations:

Ethics approval was granted by the Human Research Ethics Committee, Stellenbosch University (no: S13/07/130, main study N11/07/215). Waiver of consent was requested as the data was collected anonymously, only linking the record to a unique study number.

RESULTS

Demographics

There were 168 patients enrolled in the study. The male to female ratio was 1:1.2. The majority, namely 112 neonates (67%) were born prematurely, and 56 (33%) were full term babies.

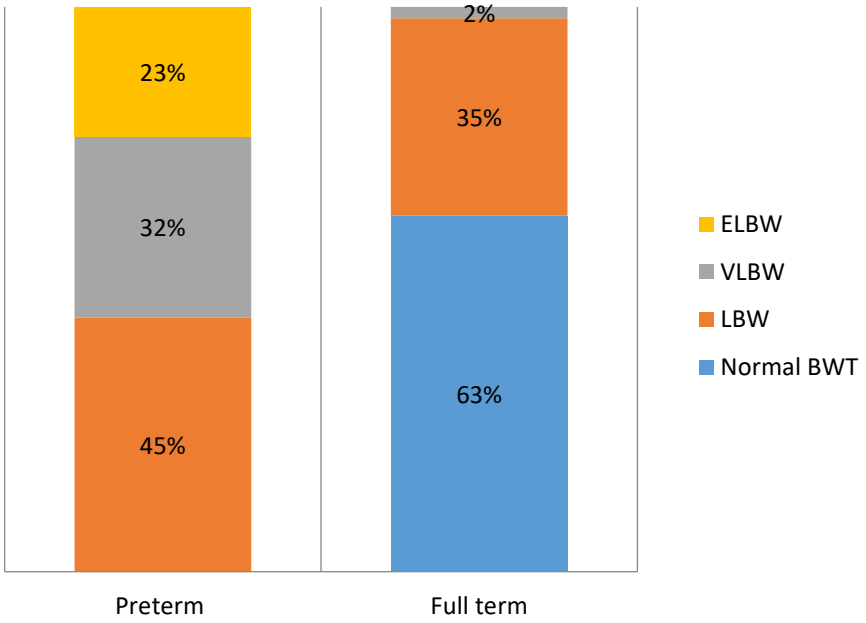

Figure 1: Representation of birth weight categories.

Nearly half (45%) of the preterm neonates had a low birth weight, 32% had a very low birth weight, 23% had an extremely low birth weight. Of the term neonates, 35% were born with a low birth weight, 2% with a very low birth weight and 63% weighed more than 2500 grams. The grouped weights had a mean weight of 2.35 kg (median 2.0 kg; standard deviation of 0.978) for the study population.

Diagnoses:

The number of diagnoses per admitted neonate ranged between 1 and 7 with a mean of 4 diagnoses per neonate. The primary diagnoses were respiratory distress of the newborn (RDS) in 20%, hyaline membrane disease (HMD) in 14%, prematurity secondary to spontaneous preterm labour (SPTL) in 10%, neonatal

hyperbilirubinemia/neonatal jaundice (NNJ) in 9% and potential risk of sepsis in 8.5%. Less common diagnoses were perinatal asphyxia (3%) , anaemia (3%), twin delivery (3%) and preterm premature rupture of membranes (3%). The other 26.5% of the diagnoses included hypoglyceamia (2%), intra-uterine growth retardation (2%), syphilis exposure (2%), feed intolerance (2%), transient tachypnea of the newborn 1%, cardiac defects 1% and thrombocytopenia 0.6%. (see chart 3)

HIV INFECTION EXPOSURE

One hundred and twenty three (73%) of the babies were HIV-unexposed , while 44 (26%) were exposed to HIV and one whose exposure was unknown (0.5%). All HIV-exposed infants, as well as those of the mother's whose HIV status was unknown, started on antiretroviral (ARV) prophylaxis. The ARV prophylaxis included nevirapine (n=44, 98%) and 1 was started on zidovudine (2%).

MEDICINES

There were 810 medicine events recorded from 168 neonates, which included 59 different medicines. Mineral supplements were included. Excluded were blood products and intravenous fluids. The range of medicines prescribed per neonate varied from 1 to 14, with an average number of 5 medicines prescribed to each study patient.

The majority of the medicine events (98.5%) involved registered medicines, with 1.5% not registered in South Africa. The unregistere medicines were intravenous phenorbarbitone (8 prescriptions) and chloral hydrate (1 prescription). Both these medicines required a section 21 application form to be filled in. A section 21 form is a form required by SAHPRA for authorization of use of an unregistered medication. .

The majority (85%;n=692) of the medicine events were off label. There was no extemporaneous use of any medicine in neonates during the study period. The number of off label drug events per neonate ranged from 1 to 15 with an average of 5 off label events per neonate. There was an average of 5 off label events in the premature group, while the term group had an average of 3 off label events per neonate. The majority (48%; n=391) of the off label prescriptions were for age, while 44% (n=356) for frequency, 37% (n=296) were off label for weight and 29% (n=236) off label for indication. In less than 2% of patients, the medicine was prescribed off

label for route and in 0.4%, off label for lack of data. Less than 1% (0.7%; n=6) involved medicines contraindicated in neonates. The reasons for off-label use per medication were analysed in groups and these often overlapped. The percentages portrayed were calculated for each group out of the 810 events.

FLOW CHART 1: GRAPHIC REPRESENTATION OF REGISTRATION AND LABELLING STATUS.

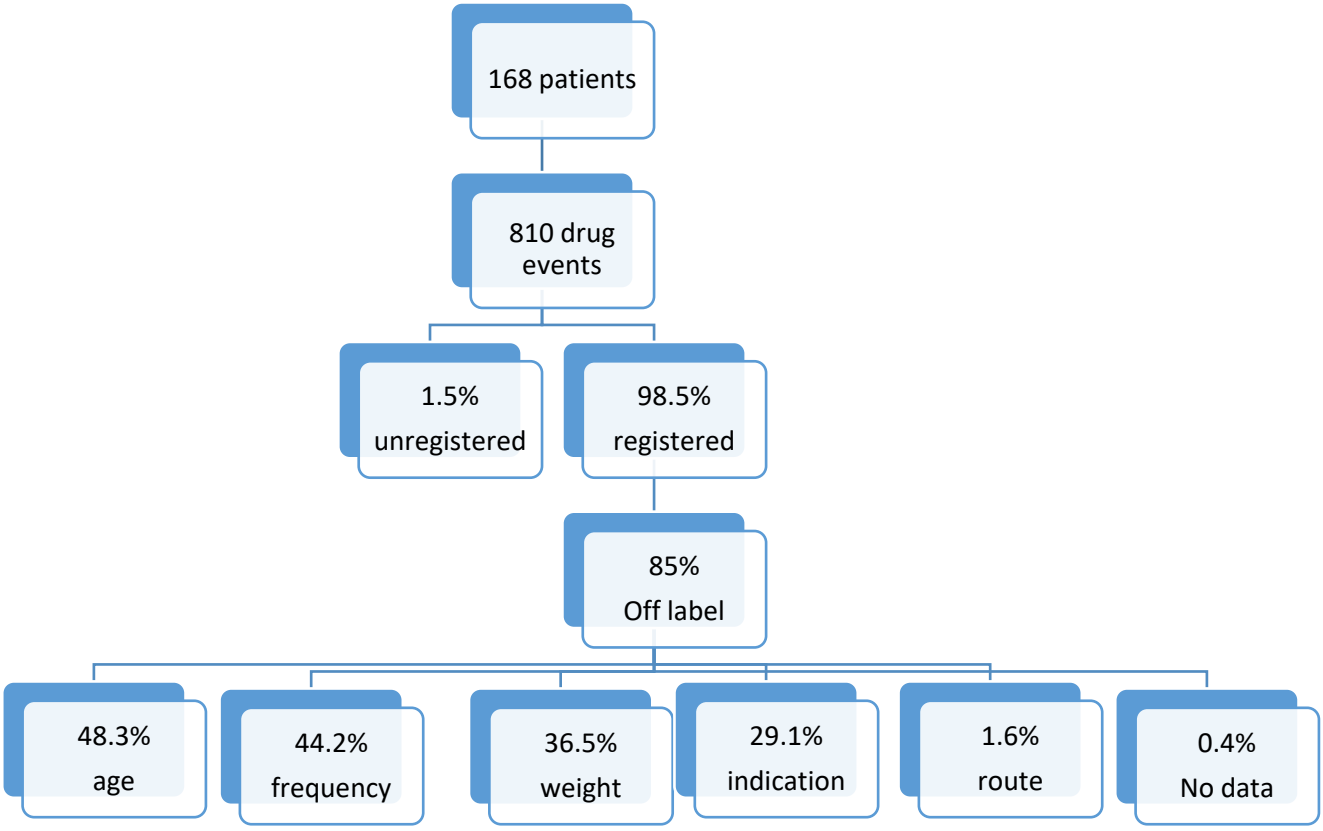

TABLE 1: The ten most commonly prescribed medicines

Medicine	Frequency of prescription events	Percentage
Penicillin G	109	13.5%
Gentamycin	104	12.9%
Aminophylline BD	97	12.0%
Aminophylline stat	83	10.3%
Caffeine	56	6.9%
Nevirapine	44	5.4%
Vitamin D	38	4.7%
Meropenem	27	3.3%
Glycerine suppository	23	2.9%
Atropine	21	2.6%

The most commonly prescribed medicines were Penicillin G (109 events) 13.5% and Gentamycin (104) 12.9%. These were used as the first line of antibiotic therapy for all neonates with confirmed or suspected sepsis. This was followed by aminophylline as a twice daily dose (n=97) 12.0% and aminophyilline as a single dose (n=83) 10.3%, Caffeine (a registered medicine) was prescribed for (n=56) 6.9% neonates. These three agents are prescribed for neonates weighing less than 1500g to prevent apnoea of prematurity. Nevirapine was prescribed for 44 neonates (5.4%) exposed to Human immunodeficiency virus in-utero. A small number (n=38; 4.7%) received vitamin D. Only 4% received meropenem, followed by Glycerine suppositories in 3% and atropine in 2.9%. Atropine was used for premature neonates with hyaline membrane disease for prevention of bradycardia during intra-tracheal incubation. Vidaylin and vancomycin prescriptions made up 2.6% each. The combination of meropenem and vancomycin were second line antibiotic therapy for neonates with sepsis. The

surfactants were prescribed for neonates admitted to the general neonatology wards with hyaline membrane disease: Curosurf (15) 2%, and Survanta (1.2%). Doxapram was prescribed in 1.5%.

Six most common off label medicines and reasons for off label use.

Medicine	**No. of prescriptions**	**Reason for off label status**
Aminophylline stat	**83 (10%)**	**Indication, age, weight for dose**
Aminophylline 12 hourly	**97 (12%)**	**Age, Indication frequency and duration**
Nevirapine	**44 (5.4%)**	**Off-label for age and weight for dose**
Meropenem	**27 (3%)**	**Age and frequency**
Chlorhexidine	**7 (0.8%)**	**Age, frequency and duration**
Azithromycin	**3 (0.4%)**	**Age, weight, dose and duration**

As demonstrated in flow diagram 1, 85% of the prescription events were off-label. The off-label events for each medication ranged from a single to 3 off label events. Intravenous aminophylline as a single or 12 hourly dose had the most off label events. Single dose aminophylline was used off label for indication, age, and weight for dose. As a twelve hourly dose, it was off label for age, indication, frequency and duration. Other medication that had 3 or more reasons for off-label classification were Azithromycin and Perfalgan. Nevirapine which is widely used for prevention of mother to child transmission of HIV was off label for age, and weight for dose. The package insert had a dose (per kilogram of weight) for children from the age of two months, there were no guidelines for prescribing to neonates. Although it is indicated for prevention of transmission, it is only registerd for use from 2 months of age.

Table 3 demonstrates all the medicines (48) prescribed in the study. It excludes mineral supplements, and classifies the medicines according to the World health organisation's Anatomical Therapeautic Chemical Classification System (ATC). It also tabulates and the drug events (753). Included on the table are medicines that are not registerd for use, those that are registered,and the reason for off label classification, if any are noted.

Table 3: Drug categories according to ATC Classification

Therapeutic class	**WHO ATC**	**Active substance**	**Number of drug events**	**Criterion of off label use**
Proton pump inhibitors	A02BC	Omeprazole	1	Age, weight for dose, no paediatric data
Enema	A06AG	Glycerine suppository	23	Age, Weight for dose.
Multivitamines	A11B	Vi-daylin	19	Age, weight for dose.
Vitamin D and analogues	A11CC	Vitamin D	38	None
Vitamin K	B02BA	Vitamin K	4	Weight for Dose,
C Cardiac therapy				
Atropine	C01E	Atropine	21	Age, weight for dose
Antifungals	D01A	Nystatin	2	Absence of Pediatric information
Silicone and zinc products	D02AA	Zinc and castor oil ointment	2	
Antibiotics	D06A	Bactroban (mupirocin)	8	

Biguanides and amides	D08AC	Chlohexidine	7	Age, frequency and duration
Prostaglandins	G02AD	Prostin E2	2	Absence of Pediatric information, Indication, dose
Glucocorticoids	H02AB	Dexamethasone	1	Indication, frequency, dose
		Hydrocortisone	1	Route, Indication, frequency, dose
Carbapenems	J01DH	Meropenem	27	Age, frequency, dose
		Ertapenem	1	
Glycopeptideantibacterials	J01XA	Vancomycin	19	Frequency, dose
Combinations of sulfonamides and trimethoprim, incl. derivatives	J01EE	Cotrimoxazole	1	Frequency, dose
Beta-lactamase resistant penicillins	J01CF	Cloxacillin	1	Dose
Beta-lactamase sensitive penicillins	J01CE	Procain Benzylpenicillin	1	
		Benzylpenicillin (Pen G)	109	
Lincosamides	J01FF	Clindamycin	1	
Aminoglycosides	J01GB	Amikacin	1	
		Genatmycin	104	
Macrolides	J01FA	Erythromycin	1	

		Azithromycin (Zithromax)	3	Frequency, dose
Drugs for treatment of tuberculosis: Antibiotics	J04AB	Isoniazide	2	Dose
J05 Antivirals				
Nucleosides and nucleotides excl. reverse transcriptase inhibitors	J05AB	Acyclovir	2	
Nucleoside and nucleotide reverse transcriptase inhibitors	J05AF	Zidovudine (AZT)	1	Frequency, dose
Non-nucleoside reverse transcriptase inhibitors	J05AG	Nevirapine	44	
Triazole derivatives	J02AC	Fluconazole	3	
Specific immunoglobulins	J06BB	Tetanus immunoglobulin	1	
Immunoglobulin, normal human, for intravenous administration	J06BA02	Polygam	8	
Bacterial vaccines	J07AM	Tetanus toxoid	1	
Choline derivatives	M03AB	Suxamethonium	1	
Other general anesthetics	N01AX	Ketamine	3	
Aldehydes and derivatives	N05CC	Chloral hydrate	1	Unregistered
Xanthine derivatives	N06BC	Caffeine	56	
Other opioids	N02AX	Tilidine (valoron)	1	Age, dose
Anilides	N02BE	Paracetamol (oral)	3	Age, dose, frequency
	N02BE	Paracetamol (IVI Perfalgan)	6	
Natural opium alkaloids	N02AA	Morphine	1	
Barbiturates and derivatives	N03AB	Phenobarbitone (IV)	8	Not registered

		Phenobarbitone (oral)	1	
Xanthines	R03DA	Aminophylline (Once off)	83	
	R03DA	Aminophylline (12 Houly)	97	
Respiratory stimulants	R07AB	Doxapram	11	Absence of Pediatric information, frequency, age, dose indication,
Lung surfactants	R07AA	Poractant alfa (curosurf)	15	
		Beractant (Survanta)	9	
Antibiotics	S01AA	Chloramphenicol	4	
Anticholinergics	S01FA	Cyclomydril	3	

DISCUSSION

A great number of studies have been done internationally that documented the prevalence and side effects of a range of medications used in the neonate and child, with very few studies from Africa (41). Off label use was a highly prevalent problem in healthcare, with rates of up to 90% reported for neonatal intensive care units (42).There were no studies available prior to this study, that divide the neonatal group based on gestational age and birth weights. That is unique to this study.

The off label use in neonates in this study was unexpectedly high (86%) if compared to a similar study in the European Union which reported a range of OL events of 46-60% (4). However, a study done in Estonia reported that 87% of all prescribed medicines to neonates were off label (490 neonates were included, with the majority of prescriptions being antibiotics, medicines for the central nervous system and

cardiovascular system (5). There was at least one off label medication prescribed per neonate in the Estonian study (5), which was similar to our study.
As noted in the article reviews, a wide range of medicines formulations were used in neonates, mostly off label, since there was little knowledge regarding the dose, formulation, and evidence of safety and efficacy (5). As mentioned, the preterm infant was even more vulnerable than the term neonate due to a further reduction in excretion and clearance when compared to term infants (39). Off label use of medication in the neonate is often a necessity as there is a lack of clinic trials that provide safety and efficacy data (13).

The most common prescribed medicines in this study were Penicilling G and Gentamycin, both antibiotics, which were similar to findings in the Estonia study, where antibiotics were more common (42)

The prescribed 1.5% of unregistered medicines in this study was low in comparison to a number of studies done worldwide. When compared to other low- to middle income contries, a Palestinian study reported a higher rate of 7.1% (42). Studies in France and the United Kingdom showed rates of 10%, In Italy 12% and rates of 14% in the Netherlands (42). A study in Europe reported that only 34% (66% unregistered) of potentially neonatal medicines were registered (13). The most commonly prescribed medication that was unregistered in the Netherlands was caffeine (13), which is a registered medication in South Africa,and also used as approved by the South African Health Products Regulatory Authourity (SAHPRA)

The most common reason for off- label use in this study was age, with 48% of the prescribed medication being used off-label for the neonatal patient. Of note was the most frequently used off-label for age medication which was Nevirapine with 49 prescription for all HIV-exposed infants. Nevirapine is only recommended for use from the age of 2 months by the South African package insert, although, there was a recommended dose per kilogram of weight. Human immunodeficiency virus is a great cause of morbidity and mortality in Africa. South Africa has a high prevalence of HIV infection with the number of people living with HIV in 2011 was 6.3 million, in 2015, the number had increased to nearly 7 million (43). The 2015 National Antenatal

Sentinel HIV and Syphillis Survey Report showed a HIV prevalence of 30.8% among women attending antenatal care clinics (43). The prevalence of HIV among pregnant women aged 15-24 years was 19.2% in 2015 (43). One hundred and ninety seven (24.5%) of the studied medication were prescribed to neonates who had HIV-infected mothers.

Off-label for frequency was second at 44.2%, this was for aminophylline which was given intravenously, every twelve hours. The most commonly used off-label for indication was also aminophylline, which was different from the findings in a Turkish study where Erythromycin and Ibuprofen were reported to be the most common medicines used off label for indication (36). The third highest reason for of label use was weight-for-dose, the use of Atropine. As previously mentioned, the World Health Organisation's guidelines recommended medication that is suitable for age, physiological condition and the child's body size (18), this recommendation was not adhered to in this insatnce. Atropine was the most used in this off-label manner, which was consistent with the findings in the Turkish study, that found that many of the registered medications were being used on neonates, at a higher dose then was recommended by the product pamphlet or leaflet (36). The least common off-label classifications were off-label for route, contraindicated and off-label for lack of data, at 1.6, 0.7 and 0.4% respectively, which differed from the Turkish study that found that the most common reason for off label use was no data or lack of information(36). A Netherlands study found caffeine to be most common medicine used off label, whereas this study found the most common medicine to be aminophylline (22%) as caffeine is registered in South Africa for use in neonates. The off label use of the antiviral nevirapine was second at 5.4%, followed by the antibiotics for systemic use, meropenem, at 3%. This differ from studies in Estonia, Australia and India where antibiotics were found the most common off label prescribed medicines (4,5)

The study group included 79% of medicine events for pre-term neonates with respectively birth weights from extreme low birth weight (<1000g)(ELBW) in 26%, 35% had very low birth weight (<1500g) and 38% had a low birth weight of less than 2500g, which was comparable to the study done in the United Kingdom (15). There was a big gap of knowledge in medication for this group of pre-term infants as they

are definitely not “small adults” though treatment decisions are often based on observational studies and often extracted from adult data (18, 19).

Conclusion

The off-label drug use in neonates was high in this study population, indicating the need for dedicated clinical trials in neonates. At the same time, the outcomes after the use of off label medicines in neonates should be published to generate knowledge about the safety and efficacy of the medicines in neonates.

There are only a few such studies published in South Africa, and although this study only confirms what is already known by people in the academic medical settings, there are still large learning opportunities in the greater medical and pharmaceutical field. Much more work still needs to be done to encourage awareness amongst doctors and nurses who care for this valnurable population. Healthcare workers need to be more aware of what and how they are prescribing medication, that off-label status of medicines means that there is no data to suggest that the medicine they are prescribing on a daily basis to neonates has been tested by the company that produced it, on the neonatal group.

Looking at the outcomes of this study that was done in a big Southern African Tertiary institution, it is important to put it in context. Busy Southern African hospitals often do not have the capacity to despence to the large numbers of patients that are born daily, on an individual basis or script. Large neonatal units such as this order medication from the pharmacy often in bulk, which is then kept as ward stock. In this manner, there is no room for pharmacists to assess and question the script based on the patient’s age, weight and the medicines labelling and registration status. This then removes a step in the control of the prescription of these medications. Further, as previously mentioned, there are no available alternates that are based on clinical trials rather then based on the experience of the clinician.

One of the great limitations of this study was the time taken to analyse the collected data, and in that time, opportunity for a follow up study looking at the long term side

effects or long term effects of the medicine that was prescribed to the neonates either off-label or unregistered was lost.

One of the greatest achievements recently in neonatal pharmaceutics was the registration of Caffeine for use in neonates either orally or intraveneously. This significantly affected the outcomes of the study as previously, caffeine was the most widely used un-registered medicine in neonates. This proves that the health and safety of the neonate is being considered and much greater care is being taken in making medicines child safe.

Doctors, nurses and pharmacists need to be aware of the labelling and registration of medication. They all need to be aware that these medicines that they use daily may not be illegal to use, but whether they are really safe in the long run is not known. I hope that with this study, I will encourage health care workers to ask more questions with each medicine they prescribe and administer to each neonate, is it safe, is it appropriate is it registered for use. I further hope that with that, more pressure will be felt by pharmaceutical companies to develop novel ways of doing ethical studies on neonates and therfore develop safer medications for the valnurable neonate with evidence base to support the use of such medicines.

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